

REMARKS

The present invention relates generally to providing fluorescent particles useful in determining analyte concentrations in aqueous solutions. The particles of the present invention incorporate dye pairs that are selected to provide advantageously large Stokes shifts (*i.e.*, the shift in wavelength between peak light absorption and peak fluorescent emission) through resonant energy transfer between the members of the dye pairs. *See, e.g.*, specification, page 13, lines 5-23. In addition, the fluorescent particles of the present invention can provide reduced quenching of the fluorescent signal. *See, e.g.*, specification, page 14, lines 12-18.

Claims 30-44 and 46 are presently pending in the application, with claims 30, 31, and 42 presently under consideration by the Examiner. Claim 42 is amended herein so that it no longer is dependent. This amendment raises no issue of new matter.

This amendment after final is accompanied by a Notice of Appeal of all pending claims. Applicants respectfully request entry of the amendment as it reduces issues upon appeal. Specifically, the amendment removes the objection to this claim.

Applicants respectfully request reconsideration of the claims in view of the foregoing amendments and the following remarks.

Non Art-Related Remarks**Objection of claim 42**

Claim 42 has been objected to as being dependent on a rejected base claim. Applicants have amended claim 42 herein to include all the limitations of claim 30. Accordingly, Applicants respectfully request that claim 42 be indicated as allowable.

Art-Related Remarks**1. 35 U.S.C. §103 rejection of claim 30 based on Sounik *et al.* and Lazzouni *et al.***

The rejection of Claim 30 as being obvious over the combination of Sounik *et al.*, EP 0391284 and Lazzouni *et al.*, U.S. 5,460,646 is respectfully traversed. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under 35

U.S.C. §103 for the rejection of claim 30. The publications cited in the rejection, considered alone or together, do not teach or suggest each and every element of the present claims. Additionally, because the Examiner ignores various claim elements in the rejection, there is no motivation offered to modify the cited publications to provide each of the elements of the present claims. Furthermore, the cited Sounik *et al.* and Lazzouni *et al.* publications are not properly citable as references under 35 U.S.C. §103 because they are non-analogous art. Finally, even if a *prima facie* case of obviousness has been established, evidence of record demonstrating the unanticipated properties of the claimed invention rebuts such *prima facie* case. Applicants, therefore, respectfully request that the rejection of claim 30 be withdrawn or reversed.

To establish a *prima facie* case of obviousness, three criteria must be met; there must be some motivation or suggestion, either in the cited publications or in knowledge available to one skilled in the art, to modify or combine the cited publications; there must be a reasonable expectation of success in combining the publications to achieve the claimed invention; and the publications must teach or suggest all of the claim limitations. MPEP § 2142. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493; 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); see also MPEP § 2142. In analyzing obviousness, the Court of Appeals for the Federal Circuit has repeatedly cautioned that:

[t]he factual inquiry... must be based upon objective evidence of record.... [T]he best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.... [P]articular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Sang-Su Lee, 277 F.3d 1338, 1343 (Fed. Cir. 2002), 61 USPQ2d 1430, 1433 (internal citations omitted).

As will be demonstrated below, the various rejections are similarly flawed for failing to teach or suggest all of the claim limitations. Specifically, none of the cited art teaches or suggests the essential first compound which is either silicon phthalocyanine bis(dimethylhexylvinylsilyloxiide) or silicon phthalocyanine bis(trihexylsilyloxiide).

A. Claim 30

The present claims relate to fluorescent particles comprising a first compound and a second compound. In claim 30, both the first and second compound comprise a pair of dimethylhexylvinylsilyloxiide or trihexylsiloxiide substituents attached to a coordinated silicon atom:

a first compound selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxiide) and silicon phthalocyanine bis(trihexylsilyloxiide); and

a second compound that is a bis(dimethylhexylvinylsilyloxiide)-substituted or bis(trihexylsilyloxiide)-substituted phthalocyanine, naphthalocyanine, or anthranlyocyanine derivative, or a bis(dimethylhexylvinylsilyloxiide)-substituted or bis(trihexylsilyloxiide)-substituted hybrid phthalocyanine derivative.

B. The primary Sounik et al. reference

The Examiner begins the obviousness rejection with the primary Sounik *et al.* publication, which discloses the concept of combining tetraazaporphin dyes for purposes of manufacturing "thin film optical media" and "optical light switch and light modulator devices." Sounik *et al.*, page 2, lines 32-35. The Examiner acknowledges that "Sounik et al. are deficient in that they do not specifically teach the use of either 'dimethylhexylvinylsiloxiide' or 'trihexylsiloxiide' as the ligands to the Si metal." Indeed, the Examiner states that "Sounik et al. only disclose a genus that encompasses Applicants' claimed compound." Office Action mailed March 16, 2005, page 3.

Thus, the primary Sounik et al. publication discloses neither the "first compound" nor the "second compound" recited in claim 30. The primary Sounik *et al.* publication also fails to teach that two compounds should be selected together for preparing a fluorescent particle.

The Examiner also acknowledges that "[t]he Sounik et al. reference is silent with regard to the size of the fluorescent particles" as recited in the present claims. *Id.* More to the point, however, is that the primary Sounik et al. publication fails even to disclose the use of tetraazaporphin dyes in a particle form.

The following table provides a compilation of the deficiencies in the Sounik *et al.* publication, relative to claim 30:

| Claim language | Deficiencies in the primary reference |
|--|--|
| 30. <u>A fluorescent particle comprising:</u> | The Sounik <i>et al.</i> publication is silent on the fluorescence of compositions, and nothing of record indicates that dyes, when formed by melting into polymers in the fashion disclosed, would retain any fluorescent properties. |
| <u>a first compound</u> selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxy) and silicon phthalocyanine bis(triethylsilyloxy); and <u>a second compound</u> that is a bis(dimethylhexylvinylsilyloxy)-substituted or bis(triethylsilyloxy)-substituted phthalocyanine, naphthalocyanine, or anthranylocyanine derivative, or a bis(dimethylhexylvinylsilyloxy)-substituted or bis(triethylsilyloxy)-substituted hybrid phthalocyanine derivative; | The Sounik <i>et al.</i> publication does not disclose any compositions having either of the claimed compounds, much less two such compounds in the same particle, as required the claim. Instead, the Sounik <i>et al.</i> publication discloses a genus comprising many thousands of possible combinations. |
| Wherein <u>the size of said fluorescent particle is between 0.1 nm and 5000 nm</u> , and wherein said first compound differs in structure from said second compound. | The Sounik <i>et al.</i> publication does not disclose any particles as the skilled artisan in the relevant art would understand that term. Rather, the publication refers to, e.g., mixing dyes with polymers and heating until a melt phase is formed, which can be molded into "suitable shapes." The Examiner has never indicated how the term "particle" is being interpreted to include any compositions within the publication. |

From its plain language, claim 30 indicates that it is not sufficient to simply place one of the individual compounds referred to in the claim into a particle; instead, the Examiner must provide a motivation to provide both compounds as recited in claim 30 as a single fluorescent particle in order to provide the instantly claimed invention. Faced with the disclosure of the

Sounik *et al.* publication (see the generic structure on page 3-4 for example), the artisan must do the following to arrive at claim 30:

- (i) select from the broad generic structure on pages 3-4 of Sounik *et al.*, the optical ligand (Z);
- (ii) select siloxy as the ligand (Z);
- (iii) select M to be Si, to provide a dimethylhexylvinylsilyloxy or trihexylsilyloxy group;
- (iv) select a second ligand (Z) on the molecule for a bis (dimethylhexylvinylsilyloxy) or a bis (trihexylsilyloxy);
- (v) combine this molecule with another that is selected from one of two choices; silicon phthalocyanine bis(dimethylhexylvinylsilyloxy) or silicon phthalocyanine bis(trihexylsilyloxy) (neither of which are disclosed in Sounik *et al.* or Lazzouni *et al.*); and
- (vi) provide this combination as a fluorescent particle of between 0.1 nm and 5000 nm in size.

C. The secondary Lazzouni *et al.* reference

The Examiner introduces the secondary Lazzouni *et al.* publication which, according to the Examiner, “teach[es] the use of silicon (IV) 2,3 naphthalocyanine bis(trihexyl-siloxide).” Office Action mailed March 16, 2005, page 3. This publication discloses the use of this compound as an ink pigment for offset lithography (Lazzouni *et al.*, column 2, lines 39-43), and that such a compound may be ground to a “particle size” of from about 5 to 7 μm to make an ink colorant (*id.*, column 5, lines 8-24).

Silicon (IV) 2,3 naphthalocyanine bis(trihexyl-siloxide) is the only compound that the Examiner asserts is disclosed by the Lazzouni *et al.* publication. Importantly, it is the combination of that single compound with the disclosure of the admittedly deficient primary Sounik *et al.* publication that the Examiner asserts renders claim 30 obvious. See, e.g., Office Action mailed March 16, 2005, page 4 (“it would have been prima facie obvious . . . to make the tetrazaporphin dye mixtures as taught by Sounik *et al.* . . . using the silicon (IV) 2,3 naphthalocyanine bis(trihexyl-siloxide) tetrazaporphin as disclosed by Lazzouni *et al.*”).

D. The cited prior art fails to teach or suggest all elements of claim 30

The rejection of claim 30 is fatally flawed because the cited prior art fails to teach or suggest all elements of claim 30. Although not specifically stated, the Examiner presumably relies on the secondary Lazzouni *et al.* publication to teach "silicon (IV) 2,3 naphthalocyanine bis(trihexyl-siloxide) tetrazaporphin" as the "second compound" of claim 30. However, there is no assertion by the Examiner that either the primary Sounik *et al.* publication or the secondary Lazzouni *et al.* publication discloses or suggests the necessary "first compound" which must be selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxy) and silicon phthalocyanine bis(trihexylsilyloxy). Indeed, there cannot be such an assertion, as neither the primary or secondary publication discloses or event suggests such a compound.

The Examiner asserts various reasons that "[i]t would have been prima facie obvious" to combine the teachings of Sounik *et al.* and Lazzouni *et al.* in the manner suggested in the rejection. Even assuming that the Examiner is correct in one or more of these assertions, this is quite simply beside the point. Even if one should "make the tetrazaporphin dye mixtures as taught by Sounik *et al.* . . . using the silicon (IV) 2,3 naphthalocyanine bis(trihexyl-siloxide) tetrazaporphin as disclosed by Lazzouni *et al.*" (*id.*, page 4), one would not arrive at the invention of claim 30.

By ignoring the "first compound selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxy) and silicon phthalocyanine bis(trihexylsilyloxy)" element of claim 30, the Examiner has not provided particular findings as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed, as required to establish a *prima facie* case of obviousness.

The Sounik *et al.* and Lazzouni *et al.* publications, considered alone or together, do not teach or suggest each and every element of the present claims. The instant case is distinguished from composition of matter selection inventions where all the elements (i.e. components) of the claim are present in the prior art but that there is a difference in the range of the amount of one or more of the added elements. For example, the Federal Circuit upheld an obviousness rejection for a nickel alloy that contained twelve additional elements when the prior art taught all elements and gave ranges that in eleven of twelve cases, completely overlapped the claimed range for

those elements. *In re Harris*, - - F.3d - - 2005 WL 1230761, (Fed. Cir. May 25, 2005). However the Federal Circuit in *In re Harris* distinguished its decision of that of *In re Peterson*, 315 F.3d 1325, 65 USPQ2d 1379 (Fed. Cir. 2003) where all the alloy elements were identified but where there were two elements with no upper limit range.

Harris points to *Peterson* to advance his position that Yoshinari's ranges are too broad to teach any specific alloy to the skilled artisan. *Peterson* discussed that a disclosed range might become too broad to teach a subset range. 315 F.3d at 1330 n. 1. A review of *Peterson* informs the court that this case does not present such a problem. In *Peterson*, the applicant claimed a single-crystal, nickel-base superalloy comprising nickel and ten additional elements. *Id.* at 1327. Eight of the ten ranges disclosed in the *Peterson* prior art (Shah) are broader than the ranges disclosed in Yoshinari. For example, Shah's range for cobalt (0-20) is twice the range allowed by Yoshinari (0-10). *Id.* at 1329. Shah also includes two elements (carbon and boron) that have no upper limits. *Id.* In contrast, Yoshinari bounds each element to a specific range, and limits the extent of those ranges by requiring at least 58% nickel. Yoshinari, col. 8, l. 20--col. 9, l. 16; col. 10, ll. 13-19. Thus, the prior art in *Peterson* was broader than in this case.

In re Harris, - - F.3d - - 2005 WL 1230761, at *3 (Fed. Cir. May 25, 2005) (emphasis in original). Unlike even the situation in *In re Petersen* where obviousness was not found, in the instant case, its not a question whether a claimed range overlaps with that the prior art, it's a question that one of the claimed elements is entirely absent from any compositions taught or fairly suggested by the prior art.

Furthermore, by simply ignoring elements of the claim, the Examiner has failed to provide any motivation to modify the cited publications as would be required to provide each and every element of the present claims. Applicants respectfully submit that, for this reason, no *prima facie* case of obviousness has been established.

E. The Sounik et al. and Lazzouni et al. publications are not analogous art, and were selected only using hindsight

According to MPEP § 2141.01, to rely on a reference under 35 U.S.C. §103, the subject matter of the reference must be "analogous prior art." This means the publication must either be in the field of applicant's endeavor, or be reasonably pertinent to the particular problem with which the inventor was concerned. Neither the Sounik *et al.* publication nor the Lazzouni *et al.* publication meets this standard.

As described above in the *Summary of the Invention*, the present invention relates to fluorescent particles that find use as fluorescent labels in ligand-receptor assays. In that art, a "fluorescent particle" is a term that refers to solid phases used as detectable fluorescent labels that are dispersible in an assay medium, as opposed to solid phases such as membranes, coated tubes, microtiter dishes, *etc.*, that are not dispersible. The particular problem to be solved was to produce "fluorescent label systems which can be tuned to specific excitation and emission wavelengths[,] . . . to minimize fluorescence quenching and to maximize fluorescence intensities." Specification, page 3, lines 10-14. The solution was achieved by Applicants through the claimed combinations of tetrazaporphyrrole-based compounds.

In contrast, the primary Sounik *et al.* publication is directed to producing tetrazaporphin dye mixtures that have "utility in optical recording media, or as a nonlinear optical component in optical light switch or light modulator devices." Sounik *et al.*, abstract. Nothing in the Sounik *et al.* publication discloses any particles, fluorescent or otherwise. Instead, the publication refers to, *e.g.*, mixing dyes with polymers and heating until a melt phase is formed, which can be molded into "suitable shapes," and to using solutions of the dyes for spraying or spin-coating to form thin films on substrates. *Id.*, page 2, final paragraph, and page 3, first paragraph. Furthermore, the Sounik *et al.* publication is silent on the fluorescence properties of tetrazaporphin dye mixtures.

Similarly non-analogous to the instantly claimed subject matter is the secondary Lazzouni *et al.* publication, directed to producing "[a]n infrared printing ink." Lazzouni *et al.*, abstract. This publication refers to mixing a phthalocyanine as a powder with a solvent to form a colorant solution. Because pigment particles "form agglomerates," the pigment must be ground to form a useful ink for offset printing. *Id.*, column 5, lines 8-24. Like Sounik *et al.*, the Lazzouni *et al.* publication is silent on the fluorescence properties of its printing inks.

Applicants respectfully submit that the skilled artisan, seeking to produce fluorescent particles for use as fluorescent labels in ligand-receptor assays, would not have considered either the Sounik *et al.* publication or the Lazzouni *et al.* publication as pertinent art, because neither publication is reasonably pertinent to the field of biocompatible fluorescent labels, or even seeks to solve any problems related to fluorescent particles.

Applicants further submit that the rejection of claim 30 over Sounik *et al.* and Lazzouni *et al.* reveals that the Examiner has fallen victim to the "subtle but powerful attraction of a hindsight-based obviousness analysis." *In re Sang-Su Lee*, 277 F.3d at 1343. The skilled artisan, seeking to solve the problem addressed by Applicants in the present application, would not be led to the use of the specific tetrazapyrrole-bases compound pairs recited in the claims based upon publications disclosing dyes for optical recording media and printer's ink.

Instead, the solution to problems related to fluorescent label systems that can be tuned to specific excitation and emission wavelengths, while minimizing fluorescence quenching and maximize fluorescence intensities, can only be gleaned in hindsight using Applicants' specification as a guide. Once the solution was obtained, the Examiner decomposed the claimed invention into its constituent elements, attempted to locate the various elements in the prior art, and then asserted that it would have been easy to reassemble such elements into the invention. Yet even then, the Examiner failed to address each and every element of the claims.

Applicants respectfully submit that, because the Sounik *et al.* and Lazzouni *et al.* publications are not properly citable as references under 35 U.S.C. §103, no *prima facie* case of obviousness has been established.

F. The rejection ignores evidence of unexpected properties

Further compounding the flaws in the rejection of claim 30 is the Examiner's misunderstanding of how evidence of unexpected properties is to be considered. In previous submissions, Applicants have discussed in detail evidence in the present specification that the claimed fluorescent particles exhibit unexpected properties that overcome any *prima facie* case of obviousness that may have been established by the Examiner. Specifically, when the dye pairs recited in the claims are included in a single fluorescent particle, fluorescence energy transfer ("FET") occurs between the members of the dye pair. As described in the instant specification on page 40, lines 10-19, FET was confirmed in the particles of the instant invention by liberation of the dyes and measuring the loss in emission intensity of the acceptor dye. The FET parameters of the particles of the present invention are described in detail in the Example beginning on page 43, line 21. In addition, as described in the instant specification on page 87, evidence is provided that incorporation of tetrazaporphin dyes in particles can result in dramatic

quenching of the fluorescence signal. The use of axial ligands such as bis(dimethylhexylvinylsiloxide) can dramatically reduce this quenching.

The Examiner believes that it is appropriate to disregard this evidence for unexpected properties because "Applicants claims are not limited to dye pairs that undergo fluorescence energy transfer." Office Action, March 10, 2004, page 10. However, the Examiner's reasoning for not considering the evidence offered in the specification is simply incorrect. The unexpected properties that are confirmed by experimental evidence in the specification result from incorporating the claimed combination of compounds into a fluorescent particle. Thus, the features upon which Applicants rely certainly are recited in the instant claims. The failure to properly consider evidence presented in the specification is itself error that renders a *prima facie* case of obviousness deficient. MPEP § 2144.08(II)(B). Applicants respectfully submit that the unexpected properties described in detail in the instant specification, properly considered, rebuts any *prima facie* case that has been established.

G. The rejection of claim 30 should be withdrawn or reversed

Because no *prima facie* case of obviousness has been established by the Examiner, or, in the alternative, because any *prima facie* case of obviousness has been rebutted by a showing of unexpected properties of the claimed invention, Applicants respectfully request that the rejection of claim 30 under 35 U.S.C. § 103 be withdrawn or reversed.

2. 35 U.S.C. §103 rejection of claim 30 based on Sounik et al., Lazzouni et al., and Brinkley et al.

The Examiner has formulated a second obviousness rejection of claim 30 which is apparently premised upon the new Brinkley *et al.* publication in combination with the same primary Sounik *et al.* and secondary Lazzouni *et al.* publications discussed in detail above. Despite including Brinkley *et al.* in the rejection of claim 30, no new rationale over that of the primary Sounik *et al.* and secondary Lazzouni *et al.* publications taken together is offered. Indeed, the relationship of the newly cited Brinkley *et al.* publication to claim 30 is not addressed in the least by the Examiner. Instead, the Examiner's remarks in the rejection concerning Brinkley *et al.* are directed entirely toward claim 31, the rejection of which is addressed *infra*.

The Brinkley *et al.* publication is cited solely for its “use of latex particles” (Office Action, mailed March 10, 2004, page 8), and not because it cures any defects in the rejection of claim 30 based on Sounik *et al.* and Lazzouni *et al.* Thus, with regard to claim 30, the many deficiencies in the rejection discussed in detail remain despite the inclusion of Brinkley *et al.* To reiterate, (1) the Sounik *et al.* and Lazzouni *et al.* publications, whether considered alone or together, do not teach or suggest each and every element of claim 30; (2) because the Examiner fails to address certain claim elements in the rejection, there is no motivation offered to modify the cited publications to provide each of the elements of the present claims; (3) the Sounik *et al.* and Lazzouni *et al.* publications are not properly citable as references under 35 U.S.C. §103 because they are non-analogous art to the present invention; and (4) even if a *prima facie* case of obviousness has been established, evidence of record demonstrating the unanticipated properties of the claimed invention rebuts that *prima facie* case.

In addition, the Examiner’s remarks in this second rejection of claim 30 are completely inconsistent with the Examiner’s remarks in the first rejection of the same claim discussed in detail above. In the second rejection, the Examiner asserts that “[f]or claim 30, Sounik *et al.* teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claim 30.” Office Action, March 16, 2005, paragraph bridging pages 7 and 8. But in the first rejection over Sounik *et al.* and Lazzouni *et al.* (without Brinkley *et al.*), the Examiner acknowledged that “Sounik *et al.* are deficient in that they do not specifically teach the use of either ‘dimethylhexylvinylsiloxide’ or ‘triethylsiloxide’ as the ligands to the Si metal” as recited in claim 30. Office Action, March 16, 2005, page 3. Applicants respectfully submit that, whatever the Sounik *et al.* publication teaches, it does not by itself render claim 30 obvious, despite the Examiner’s apparent confusion on the subject.

Because no *prima facie* case of obviousness has been established by the Examiner, or, in the alternative, because any *prima facie* case of obviousness has been rebutted by a showing of unanticipated properties of the claimed invention, Applicants respectfully request that the second rejection of claim 30 under 35 U.S.C. § 103 be withdrawn or reversed.

3. 35 U.S.C. §103 rejection of claim 31 based on Sounik *et al.*, Lazzouni *et al.*, and Brinkley *et al.*

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness under 35 U.S.C. §103 for the rejection of claim 31. The publications cited in the rejection, considered alone or together, do not teach or suggest each and every element of this claim. Additionally, because the Examiner ignores various claim elements in the rejection, there is no motivation offered to modify the cited publications to provide each of the elements of the claim. Furthermore, while the Brinkley *et al.* publication is in an analogous art to the present invention, the cited Sounik *et al.* and Lazzouni *et al.* publications are not, and their combination can only be made through the improper use of hindsight. Applicants therefore respectfully request that the rejection of claims 31 be withdrawn or reversed.

A. Claim 31

Dependent claim 31 differs from claim 30 discussed above, in that claim 31 refers to a specific type of fluorescent particle:

“A fluorescent particle according to claim 30, wherein said particle is a latex particle.”

Thus, claim 31 describes a fluorescent latex particle comprising:

a first compound selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxy) and silicon phthalocyanine bis(trihexylsilyloxy); and

a second compound that is a bis(dimethylhexylvinylsilyloxy)-substituted or bis(trihexylsilyloxy)-substituted phthalocyanine, naphthalocyanine, or anthranylocyanine derivative, or a bis(dimethylhexylvinylsilyloxy)-substituted or bis(trihexylsilyloxy)-substituted hybrid phthalocyanine derivative.

B. The Sounik et al. and Lazzouni et al. references

As discussed above, the Examiner acknowledges that “Sounik et al. are deficient in that they do not specifically teach the use of either ‘dimethylhexylvinylsiloxy’ or ‘trihexylsiloxy’ as the ligands to the Si metal.” Office Action, March 16, 2005, page 3. The secondary Lazzouni *et al.* publication is cited by the Examiner for “teach[ing] the use of silicon (IV) 2,3 naphthalocyanine bis(trihexyl-siloxy).” Office Action, March 16, 2005, page 3. It is undisputed that neither the Sounik *et al.* publication or the Lazzouni *et al.* publication disclose or suggest the use of latex particles, as required by claim 31.

In rejecting claim 30, the Examiner asserts that "it would have been prima facie obvious . . . to make the tetrazaporphin dye mixtures as taught by Sounik et al. . . . using the silicon (IV) 2,3 naphthalocyanine bis(trihexyl-siloxide) tetrazaporphin as disclosed by Lazzouni et al."). Office Action, March 16, 2005, page 4. This same basis for combining the Sounik *et al.* and Lazzouni *et al.* references is "incorporated in its entirety" into the present rejection of claim 31 by the Examiner. Office Action, March 16, 2005, paragraph bridging pages 7 and 8.

As discussed by Applicants in detail herein above, however, even if one should "make the tetrazaporphin dye mixtures as taught by Sounik et al. . . . using the silicon (IV) 2,3 naphthalocyanine bis(trihexyl-siloxide) tetrazaporphin as disclosed by Lazzouni et al." (*id.*, page 4), one would still not arrive at the invention of claim 30. Since claim 31 incorporates all of the limitations of claim 30, this same fatal flaw similarly contaminates the rejection of claim 31.

C. The new secondary Brinkley et al. reference

The newly cited Brinkley *et al.* publication discloses that latex particles "incorporating a series of two or more fluorescent dyes having overlapping excitation and emission spectra allowing efficient energy transfer" may be used to provide "biocompatible particles" for use as labels in, for example, immunoassays and nucleic acid assays. *See, e.g.,* Brinkley *et al.*, Abstract and column 1, lines 31-45. Notably, Brinkley *et al.* is not cited to teach or suggest any compounds within the scope of the "first compound" or "second compound" referred to in claim 31.

Although the rejection is not constructed in this form, the Examiner apparently uses the new Brinkley *et al.* publication as the primary reference in rejecting claim 31, stating that "[i]t would have been obvious . . . to use the fluorescent dyes as disclosed by the combined teachings of Sounik et al. and Lazzouni et al. into 'the microparticles incorporating a series of two or more fluorescent dyes' as disclosed by Brinkley et al." Office Action, March 16, 2005, page 8.

D. The cited prior art fails to teach or suggest all elements of claim 31

Like the rejection of claim 30, the rejection of claim 31 ignores claim elements; There is no assertion by the Examiner that any publication of record, including Sounik et al. Lazzouni et al. or even the newly cited Brinkley et al. publication, discloses or suggests a "first compound" selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxyde)

and silicon phthalocyanine bis(trihexylsilyloxy), much less a motivation to combine such a “first compound” with a specified “second compound” to provide a fluorescent particle. The use of latex particles in the Brinkley *et al.* publication does not cure any of the many flaws in the Examiner’s alleged *prima facie* case demonstrated above. Instead, all of the flaws in the *prima facie* case based upon “the combined teachings of Sounik *et al.* and Lazzouni *et al.*” are “incorporated by reference” into the rejection of claim 31 by the Examiner. Should one, as the Examiner alleges “use the fluorescent dyes as disclosed by the combined teachings of Sounik *et al.* and Lazzouni *et al.* into ‘the microparticles incorporating a series of two or more fluorescent dyes’ as disclosed by Brinkley *et al.*,” one would not arrive at the invention of claim 31.

Again, in addition to the failure to teach or suggest all the elements of the claim, the Examiner also has failed to provide particular findings as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed, as required to establish a *prima facie* case of obviousness.

E. The Sounik et al. and Lazzouni et al. publications are not analogous art

As discussed herein, to rely on a reference under 35 U.S.C. §103, the subject matter of the reference must be “analogous prior art.” This means the publication must either be in the field of applicant’s endeavor, or be reasonably pertinent to the particular problem with which the inventor was concerned. While the Brinkley *et al.* publication appears to meet this standard, neither of the two other publications the Examiner seeks to combine with Brinkley *et al.* meet this standard.

As described above in the *Summary of the Invention*, the present invention relates to fluorescent particles that find use as fluorescent labels in ligand-receptor assays. In that art, a “fluorescent particle” is a term that refers to solid phases used as detectable fluorescent labels that are dispersible in an assay medium, as opposed to solid phases such as membranes, coated tubes, microtiter dishes, *etc.*, that are not dispersible. The particular problem to be solved was to produce “fluorescent label systems which can be tuned to specific excitation and emission wavelengths[,] . . . to minimize fluorescence quenching and to maximize fluorescence intensities.” Specification, page 3, lines 10-14. The solution was achieved by Applicants through the claimed combinations of tetrazapyrrole-based compounds.

The Brinkley *et al.* publication appears to be analogous art, as it is both in the field of Applicants' endeavor, and is reasonably pertinent to the particular problem with which the inventor was concerned. Like the particles of the present invention, the "fluorescent microparticles" disclosed in the Brinkley *et al.* publication are dispersible solid phases intended for use in ligand-receptor assays. *See, e.g.,* Brinkley *et al.*, column 1, lines 31-51.

Brinkley *et al.* discloses a laundry list of potential dye compound classes for use in the microparticles, the list including a general reference to "phthalocyanines":

Typically, the dyes are selected from the same family, such as the polyazaindacenes or coumarins described above. Other suitable families of dyes include hydrocarbon and substituted hydrocarbon dyes; scintillation dyes (usually oxazoles and oxadiazoles); aryl- and heteroaryl-substituted polyolefins (C2 -C8 olefin portion); carbocyanines; **phthalocyanines**; oxazines; carbostyryl; and porphyrin dyes (see Table 3). It is also possible, however, to achieve efficient energy transfer between dyes that are structurally different such as between polyolefinic dyes and dipyrrometheneboron difluoride dyes (Ex. 6); coumarin dyes and dipyrrometheneboron difluoride dyes (Ex. 7); polyolefinic dyes and coumarin dyes; dipyrrometheneboron difluoride dyes and oxazine dyes; and many others.

Brinkley *et al.*, column 11, lines 38-54 (emphasis added). The Examiner seeks to combine the Brinkley *et al.* publication with the "combined teachings" of Sounik *et al.*, directed to producing tetrazaporphin dye mixtures that have "utility in optical recording media, or as a nonlinear optical component in optical light switch or light modulator devices" (Sounik *et al.*, Abstract), and Lazzouni *et al.*, directed to producing "[a]n infrared printing ink" (Lazzouni *et al.*, Abstract). However, as already discussed, neither of these publications discloses any particles, fluorescent or otherwise, that are in any way related to the "fluorescent microparticles" disclosed in the Brinkley *et al.* publication. Indeed, neither publication discusses fluorescence at all.

Applicants respectfully submit that the skilled artisan, seeking to produce fluorescent particles for use as fluorescent labels in ligand-receptor assays, would not have considered either Sounik *et al.* publication or the Lazzouni *et al.* as pertinent art; Publications disclosing dyes for optical recording media and printer's ink are not reasonably pertinent to the field of biocompatible fluorescent labels, and do not seek to solve any problems related to such fluorescent particles. Thus, their combination with the Brinkley *et al.* publication is inadequate to support a *prima facie* case of obviousness.

F. The obviousness analysis suffers from the improper use of hindsight

Applicants further submit that the suggested combination of the Brinkley *et al.* publication with Sounik *et al.* and Lazzouni *et al.* for the rejection of claim 31 emphatically demonstrates that the Examiner has fallen victim to the “subtle but powerful attraction of a hindsight-based obviousness analysis.” *In re Sang-Su Lee*, 277 F.3d at 1343.

As seen in the quoted portion reproduced above, the generic term “phthalocyanine” is one of a large number of “dye families” recited in the Brinkley *et al.* publication. Brinkley *et al.* also provides a discussion of the properties that should be considered when selecting dyes from amongst the various dye families for incorporation into microparticles. These properties include the excitation and emission spectra of the dyes to be combined, noting that “[t]he spectral properties . . . should be determined in the polymeric materials in which they will be used (column 5, lines 46-57); the overlap of these spectra (column 5, lines 33-36); the quantum yield of the dyes to be combined, (column 5, line 65, through column 6, line 3), *etc.*

To arrive at the invention of claim 31, the skilled artisan, without reference to the present specification, would have to:

- (1) select phthalocyanines from the laundry list of potential compound families disclosed in Brinkley *et al.* for incorporation into a latex particle of between 0.1 nm and 5000 nm in size;
- (2) after making this selection, select from Sounik *et al.* (i) a tetrazaporphin with the optional ligand (Z), (ii) select siloxy as the ligand (Z), (iii) select M to be Si, to provide a dimethylhexylvinylsilyloxy or trihexylsilyloxy group, (iv) select a second ligands (Z) on the molecule for a bis (dimethylhexylvinylsilyloxy) or a bis (trihexylsilyloxy);
- (3) decide that one such compound should be the one compound the Examiner identifies in Lazzouni *et al.*; and
- (4) combine this compound with another that is selected from one of two choices; silicon phthalocyanine bis(dimethylhexylvinylsilyloxy) or silicon phthalocyanine bis(trihexylsilyloxy) (neither of which are disclosed in Sounik *et al.*, Lazzouni *et al.* or Brinkley *et al.*).

The Examiner offers a number of potential “motivations” to “use the fluorescent dyes as disclosed by the combined teachings of Sounik et al. and Lazzouni et al. into ‘the microparticles incorporating a series of two or more fluorescent dyes’ as disclosed by Brinkley et al.” Office Action, March 16, 2005, page 8. These “motivations” include solubility in organic solvents, favorable absorption characteristics including light fastness, and strong absorption peaks in the near-IR. *Id.*, pages 8-9. However, none of the properties referred to by the Examiner are in any way related to the selection criteria provided by the Brinkley et al. publication for compounds suitable for use in their microparticles, and none of the selection criteria discussed in the Brinkley et al. publication are ever considered in either Sounik et al. or Lazzouni et al.

Thus, the “motivations” relied upon by the Examiner would not lead the skilled artisan to modify the teachings of the Brinkley et al. publication with “the combined teachings of Sounik et al. and Lazzouni et al.” as the Examiner appears to assert. And yet, even with the benefit of hindsight, the Examiner fails to address each element of the claims, choosing instead to simply ignore the “first compound” selected from the group consisting of silicon phthalocyanine bis(dimethylhexylvinylsilyloxiide) and silicon phthalocyanine bis(trihexylsilyloxiide).

Applicants respectfully submit that, because the only motivation to combine the cited publications is the hindsight gained by the Examiner from Applicants’ own specification, no *prima facie* case of obviousness has been established.

G. The rejection of claim 31 should be withdrawn or reversed

Because no *prima facie* case of obviousness has been established by the Examiner, or, in the alternative, because any *prima facie* case of obviousness has been rebutted by a showing of unanticipated properties of the claimed invention, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn or reversed.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address

and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date June 3, 2005

By



FOLEY & LARDNER LLP

Customer Number: 30542

Telephone: (858) 847-6722

Facsimile: (858) 792-6773

Barry S. Wilson

Registration No. 39,431

For

Richard J. Warburg

Registration No. 32,327